

# High Pathogenicity Avian Influenza

*Fowl Plague, Grippe Aviaire*

Last Updated: January 8, 2009



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## Importance

Avian influenza viruses are highly contagious, extremely variable viruses that are widespread in birds, particularly wild waterfowl and shorebirds. Most of these viruses, which are usually carried asymptotically by wild birds, cause only mild disease in poultry. Others, the high pathogenicity avian influenza (HPAI) viruses, can kill up to 90-100% of a poultry flock. Epidemics of high pathogenicity avian influenza can spread rapidly, devastate the poultry industry and result in severe trade restrictions. HPAI viruses have been eradicated from domesticated poultry in many nations including the U.S.; however, these viruses can be reintroduced in imported poultry, wild birds or pet birds. Some avian influenza viruses can also infect mammals including humans. The severity of zoonotic avian influenza varies with the virus. Although many human infections are limited to conjunctivitis or mild respiratory disease, some viral strains cause severe disease and death. Generally, avian influenza viruses do not spread efficiently in mammals, and infections are limited to individual animals or small groups. However, some viruses can become adapted to a new species and cause epidemics or pandemics.

Currently, the world is experiencing an extensive HPAI outbreak, with no immediate prospects for complete, worldwide eradication. In 2003, HPAI viruses of the H5N1 subtype appeared in poultry in several nations in Southeast Asia. Although at times this epidemic appeared to be under control, eradication was never complete. The outbreaks continued to smolder and spread, and eventually avian H5N1 viruses reached other parts of Asia, Europe, Africa and the Middle East. The avian H5N1 strains responsible for this epidemic appear to be unusually virulent. As of January 2009, they have been responsible for approximately 390 human infections, generally as the result of close contact with poultry; about two thirds of these cases were fatal. These H5N1 viruses can also cause disease in mammals of other species, including tigers, leopards, housecats, dogs, palm civets and stone martens. In addition, numerous deaths have been reported in migratory wild birds, which usually carry avian influenza viruses asymptotically, and lethal infections have been reported in songbirds. There are fears that an avian H5N1 virus could eventually become adapted to humans, resulting in a severe human pandemic.

## Etiology

Avian influenza results from infection by viruses in the influenza virus A genus of the family Orthomyxoviridae. These viruses are also called type A influenza viruses. In addition to avian influenza viruses, this genus includes the closely related human, equine, swine and canine influenza viruses.

Two surface antigens, the hemagglutinin (H) and neuraminidase (N) proteins, are used to classify type A influenza viruses into subtypes. There are 16 hemagglutinin antigens (H1 to H16) and nine neuraminidase antigens (N1 to N9). Waterfowl and shorebirds, which seem to be the natural reservoirs for the type A influenza viruses, carry all of the known H and N antigens and, thus, can theoretically carry all subtypes. The predominant subtypes in wild waterfowl change periodically. In North America, subtypes containing H3, H4 and H6 are found most often in wild ducks, but H5, H7 and H9 viruses are also found at low levels. From 1993 to 2000, subtypes containing H1 to H7 and H9 to H11 were isolated from live bird markets in the northeastern U.S. Limited information is available on the subtypes present in birds other than poultry and waterfowl. H3N2, H4N2, H4N6, H5N1, H5N2, H5N9, H7N1, H7N3, H9N2, H10N4 and H10N7 have been found in ratites. Isolates from cage birds usually contain H3 or H4. Natural or experimental infections with subtypes containing H7 or H5 have also been demonstrated in some species of passerine and psittacine birds.

Avian influenza viruses are classified as either HPAI or low pathogenicity avian influenza (LPAI) viruses, based on the genetic features of the virus and the severity of disease in poultry. To date, only subtypes containing H5 or H7 have been highly pathogenic; subtypes that contained other hemagglutinins have been found only in the LPAI form. H5 and H7 LPAI viruses also exist, and these strains can evolve into high pathogenicity strains.

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## **Antigenic shift and drift in influenza A viruses**

Type A influenza viruses can change frequently. Strains evolve as they accumulate point mutations during virus replication; this process is sometimes called 'antigenic drift'. A more abrupt change can occur during genetic reassortment. Reassortment is possible whenever different influenza viruses infect a cell simultaneously; when the new viruses (the 'progeny') are assembled, they may contain some genes from one parent virus and some genes from the other. Reassortment between two different strains results in the periodic emergence of novel strains. Reassortment between subtypes can result in the emergence of a new subtype. Reassortment can also occur between avian, swine, equine and human influenza A viruses. This type of reassortment can result in a 'hybrid' virus with, for example, both avian and human influenza virus proteins.

An abrupt change in the subtypes found in host species is called an 'antigenic shift.' Antigenic shifts can result from three mechanisms: 1) genetic reassortment between subtypes, 2) the direct transfer of a whole virus from one host species into another, or 3) the re-emergence of a virus that was found previously in a species but is no longer in circulation. Antigenic drift and antigenic shifts result in the periodic emergence of novel influenza viruses. By evading the immune response, these viruses can cause influenza epidemics and pandemics.

## **Avian influenza virus infections in mammals**

Avian influenza viruses are closely related to type A influenza viruses found in humans, horses, pigs and dogs. Ordinarily, the influenza viruses found in each species infect only that species. However, occasionally a virus from one species may infect another species. This can happen in two ways. If two viruses from different species infect a cell simultaneously, the gene segments can reassort when new virus particles are assembled. For example, if a cell is infected by an avian and a human influenza virus, the new viruses budding from that cell might contain some segments from the avian influenza virus and others from the human influenza virus. An avian influenza virus that contained some genes from a human influenza virus might be able to establish itself in humans. Sometimes, an influenza virus can also jump 'whole' from one species to another. For instance, avian influenza viruses have been known to jump from birds into people, cats, mink, seals, horses and other animals. Usually, the virus is poorly adapted to the new species, cannot be transmitted efficiently, and quickly dies out.

Occasionally, a virus develops new mutations that help it replicate and be transmitted in the new host species, and a permanent jump is made. Although cross-species transmission is a rare event, it may be followed by an epidemic or pandemic, since the new host has no immunity to the new virus. For an epidemic to occur, three requirements must be met: 1) a new influenza virus

subtype must emerge in a species with little or no immunity to that subtype, 2) the virus must produce disease in that species, and 3) there must be sustainable transmission in the new species. As of January 2009, the currently circulating avian H5N1 viruses have met the first two criteria in humans and cats, but efficient or sustainable transmission has not been reported in either species.

## **Geographic Distribution**

H5N1 viruses have been eradicated from domesticated poultry in most developed nations, but reservoirs for these viruses occur worldwide in wild birds.

The current (2003-2009) avian H5N1 outbreak began in poultry in Southeast Asia in 2003. From 2003 to 2008, it spread into domesticated or wild birds in other regions of Asia as well as parts of Europe, the Pacific, the Middle East and Africa. Although some countries have eradicated the virus from their domesticated poultry, this epidemic is ongoing and worldwide eradication is not expected in the short term.

## **Transmission**

In birds, avian influenza viruses are shed in the feces as well as in saliva and nasal secretions. The feces contain large amounts of virus, and fecal-oral transmission is usually the predominant means of spread in wild bird reservoirs. However, some recent isolates of H5N1 have been found in higher quantities in tracheal samples than feces, suggesting that in some avian species, the primary means of transmission for this virus may no longer be the fecal-oral route. Once an avian influenza virus has entered a poultry flock, it can spread on the farm by both the fecal-oral route and aerosols, due to the close proximity of the birds. Fomites are important in transmission, and flies may act as mechanical vectors. Avian influenza viruses can persist in some environments for weeks, and they have been isolated from the water in ponds where ducks swim. H5N1 viruses have also been found in the yolk and albumen of eggs from infected hens. Although these eggs are unlikely to hatch, broken shells could transmit the virus to other chicks in the incubator.

In countries where H5N1 has been eradicated from domesticated poultry, the disease can be introduced into flocks by migratory waterfowl as well as infected poultry, pet birds or fomites. Until recently, wild birds were thought to carry only the low pathogenicity form of avian influenza viruses. Once they were introduced into poultry, these viruses recombined or mutated to produce H5N1 viruses. However, some migratory waterfowl appear to carry and disseminate the currently circulating, high pathogenicity H5N1 strains. Whether these birds can migrate long distances after being infected is controversial. H5N2 viruses have also been detected in some asymptomatic wild ducks and geese in Africa.

Some avian influenza virus strains can be transmitted to mammals by direct or indirect contact. Close contact with dead or sick birds seems to be the principal means of

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transmission to humans; however, a few cases may have resulted from exposure to contaminated feces, and swimming in contaminated water is theoretically a source of exposure. Transmission by ingestion has been reported rarely in humans, felines and dogs. Two people became infected with an avian H5N1 virus after eating uncooked duck blood. One avian H5N1 infection occurred in a dog that had eaten infected duck carcasses. Similarly, leopards and tigers in zoos, as well as housecats, were probably infected with avian H5N1 when they ate raw birds. Recently, subclinical infections were reported in cats that had been exposed to a sick swan; the most likely route was ingestion of bird feces while grooming, but aerosol transmission could not be ruled out. Experimental infections have been established in cats by intratracheal inoculation with avian H5N1 viruses and by feeding them H5N1-infected chicks. Dogs, pigs and foxes have been infected experimentally with avian H5N1 viruses via respiratory exposure. Pigs and foxes have also been inoculated by feeding infected poultry tissues. Cattle can be infected by intranasal inoculation of H5N1 viruses isolated from cats.

Cats and experimentally infected foxes appear to shed this virus from the intestinal tract as well as the respiratory tract. Fecal shedding of the avian H5N1 virus has also been documented in a child with diarrhea. In experimentally infected dogs, avian H5N1 viruses have been found in respiratory secretions, but fecal shedding has not been seen. Pigs and cattle can shed these viruses by the respiratory route. Raccoons have not been inoculated with avian H5N1, but animals that were infected with an avian LPAI H4N8 virus shed it only from the respiratory tract.

Limited animal-to-animal transmission appears to have occurred in zoo tigers, as well as in experimentally infected housecats in some studies. No animal-to-animal transmission was reported in the asymptomatic cats infected by exposure to a sick swan, or in experimentally infected pigs. In one study, avian H5N1 virus was not transmitted to one dog or three cats in contact with four experimentally infected dogs, or to three dogs in contact with infected cats. In humans, a few cases of limited person-to-person spread have been documented after close, prolonged contact. Sustained human-to-human transmission has not been reported, as of January 2009. Viral antigens and nucleic acids were detected in the fetus of a pregnant woman who died of avian H5N1, suggesting that transplacental transmission may be possible in some species.

## Disinfection

Although avian influenza viruses are enveloped, some of these viruses have been reported to survive for long periods in the environment, particularly when the temperature is low. Virus survival in the environment is influenced by temperature, pH, salinity and the presence of organic material. Currently, there is no consensus on survival times. In one study, LPAI viruses survived in distilled water for more than 100 days at 28°C (82°F) and

200 days at 17°C (63°F). In another study, LPAI viruses remained viable for at least 35 days in peptone water at 4°C (39°F), 30°C (86°F) or 37°C (98.6°F). Various avian influenza viruses were reported to survive for four weeks at 18°C (64°F). A few studies have examined virus persistence in feces. In one study, LPAI H7N2 viruses persisted for up to two weeks in feces and on cages. The H7N2 viruses could also survive for up to 32 days at 15-20°C (59-68 °F), and at least 20 days at 28-30°C (82-86°F). In other studies, LPAI viruses were reported to survive for at least 44 or 105 days in feces. One recent study examined the persistence of HPAI viruses. H5 and H7 HPAI viruses seemed to survive for shorter periods in water than LPAI viruses; however, they persisted in fresh water for 100 days or more at 17°C (63°F) and for approximately 26-30 days at 28°C (82°F). Avian influenza viruses can survive indefinitely when frozen.

The influenza viruses are susceptible to a wide variety of disinfectants including sodium hypochlorite, 70% ethanol, oxidizing agents, quaternary ammonium compounds, aldehydes (formalin, glutaraldehyde, formaldehyde), phenols, acids, povidone-iodine and lipid solvents. They can also be inactivated by heating to 56°C (133°F) for a minimum of 60 minutes, as well as by ionizing radiation or low pH (pH 2).

## Infections in Humans

### Incubation Period

The incubation period for avian influenza is difficult to determine in humans. Human influenza viruses usually cause disease after 2 to 3 days. However, limited data from H5N1 avian influenza virus infections suggest that the incubation period for this virus may range from two to eight days and could be as long as 17 days. The World Health Organization (WHO) currently suggests using an incubation period of seven days for field investigations and monitoring patient contacts.

### Clinical Signs

Rare infections with various avian influenza virus subtypes have been reported in humans. Healthy children and adults, as well as those with chronic medical conditions, have been affected. While some infections have been limited to conjunctivitis and/or typical influenza symptoms, others were serious or fatal. Viral pneumonia, acute respiratory distress syndrome, severe bronchointerstitial pneumonia, multiple organ dysfunction and other severe or fatal complications have been reported. HPAI viruses appear to cause more severe infections than LPAI viruses.

The currently circulating avian H5N1 (HPAI) strains tend to cause high fever and upper respiratory symptoms resembling human influenza as the initial signs. In some patients, there may be chest pain, bleeding from the nose and gums, or gastrointestinal symptoms such as diarrhea,

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vomiting and abdominal pain. Respiratory signs are not always present at diagnosis. Two patients from southern Vietnam had acute encephalitis without respiratory symptoms. Similarly, a patient from Thailand exhibited only fever and diarrhea. Many patients develop lower respiratory tract disease soon after the onset of illness; the symptoms may include dyspnea, hoarseness of the voice and crackles during inspiration. The respiratory secretions and sputum are sometimes blood-tinged. Most patients deteriorate rapidly. Multiorgan dysfunction is common in the later stages, and disseminated intravascular coagulation can occur.

The following human infections with avian influenza viruses were reported from 1997 to 2008:

- In 1997, eighteen human infections were reported during a H5N1 HPAI outbreak among poultry in Hong Kong. The symptoms included fever, sore throat and cough and, in some cases, severe respiratory distress and viral pneumonia. Eighteen people were hospitalized and six died.
- In 1999, avian influenza (LPAI H9N2) was confirmed in two children in Hong Kong. The illnesses were mild and both children recovered. No other cases were found. Six unrelated H9N2 infections were also reported from mainland China in 1998-1999; all six people recovered.
- In 2002, antibodies to an avian H7N2 virus were found in one person after a LPAI outbreak in poultry in Virginia.
- In 2003, two HPAI H5N1 infections were reported in a Hong Kong family that had traveled to China. One of the two people died. Another family member died of a respiratory illness while in China, but no testing was done.
- In 2003, 347 total and 89 confirmed human infections were associated with an outbreak of H7N7 HPAI in poultry in the Netherlands. Most cases occurred in poultry workers, but three family members also became ill. In 78 of the confirmed cases, conjunctivitis was the only sign of infection. Two people had influenza symptoms such as fever, coughing and muscle aches. Five had both conjunctivitis and influenza-like illnesses. (Four cases were classified as "other.") The single death occurred in an otherwise healthy veterinarian who developed acute respiratory distress syndrome and other complications. His initial symptoms included a persistent high fever and headache but no signs of respiratory disease. The virus isolated from the fatal case had accumulated a significant number of mutations, while viruses from most of the other individuals had not.
- In 2003, a LPAI H9N2 avian influenza virus infection was confirmed in a child in Hong Kong.

The symptoms included mild fever, mild dehydration and cough. The child was hospitalized but recovered.

- In 2003, a LPAI H7N2 infection with respiratory signs was reported in a patient in New York. The person, who had serious underlying medical conditions, was hospitalized but recovered.
- In 2004, two cases of conjunctivitis and flu-like symptoms were confirmed in poultry workers in Canada. One virus was LPAI; the other was HPAI. Both people recovered after treatment with an antiviral drug. Ten other infections were suspected but not confirmed; these cases included both conjunctivitis and upper respiratory symptoms. All of the infections were associated with a H7N3 virus outbreak in poultry.
- From 2004 to 2008, sporadic human illness and deaths were associated with widespread outbreaks of HPAI (H5N1) among poultry. As of January 7 2009, 393 confirmed human cases had been reported to WHO; 248 cases were fatal. Human infections were reported from several countries in Asia. A few cases occurred in Africa, Azerbaijan, the Middle East and Turkey.
- In 2007, a mild case of LPAI H9N2 virus infection was reported in a 9-month-old child in Hong Kong.

## Communicability

Rare cases of probable person-to-person transmission, and no cases of sustained transmission, have been reported in humans infected with avian influenza viruses. Fecal shedding of the avian H5N1 virus has been documented in a child with diarrhea. Transplacental transmission of this virus may be possible.

## Diagnostic Tests

Avian influenza viruses can be identified by reverse transcription polymerase chain reaction (RT-PCR) tests, antigen detection or virus isolation. In the U.S., samples that test positive by RT-PCR or antigen tests are confirmed by the Centers for Disease Control and Prevention (CDC). RT-PCR and antigen testing of avian influenza viruses must be carried out in Biosafety Level (BSL) 2 laboratory conditions. BSL 3+ laboratory conditions are required for the isolation of the HPAI viruses. Serology has been used for surveillance.

## Treatment

Four antiviral drugs -- amantadine, rimantadine, zanamivir, and oseltamivir - are active against the human influenza viruses. Studies suggest that these drugs may also be helpful in avian influenza infections in humans. Limited evidence suggests that some of these drugs, particularly oseltamivir, may increase the chance of survival in patients infected with avian H5N1 viruses if the drugs are given within 48 hours of the onset of symptoms. However, further testing, particularly on the optimum dose and duration of treatment, is still needed.

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Drug resistance develops rapidly in viruses exposed to amantadine or rimantadine, and may emerge during treatment. Most avian H5N1 viruses that have caused illness in humans during the current epidemic are resistant to amantadine and rimantadine. Although resistance to zanamivir and oseltamivir has been reported in these viruses, it is currently uncommon.

## Prevention

Controlling epidemics in poultry decreases the risk of exposure for humans. People working with infected birds should follow good hygiene practices and wear appropriate protective clothing such as boots (or shoe covers), coveralls, gloves, respirators and goggles. The specific recommendations may vary with the virus. In addition, WHO recommends prophylaxis with antiviral drugs in people who cull birds infected with H5N1 HPAI viruses. To prevent reassortment between human and avian influenza viruses, people in contact with infected birds should be vaccinated against human influenza. They are also discouraged from having contact with sick birds while suffering flu symptoms.

In areas where H5N1 could be present in domesticated poultry, poultry farms and live bird markets should be avoided. Precautions should also be taken when handling raw meat and eggs, which can contain virus. Sanitary precautions and cooking methods recommended to destroy *Salmonella* and other poultry pathogens are sufficient to kill avian influenza viruses. The hands should be washed thoroughly with soap and warm water after handling meat or eggs. Cutting boards and utensils should be washed with soap and hot water. Poultry should be cooked to a temperature of at least 74°C (165°F). Eggs should be cooked until the whites and yolks are both firm.

Avian influenza viruses can be carried in wild birds, and these birds could be the initial source of infection in an area. Wild birds should be observed from a distance; close contact is discouraged. If birds or potentially contaminated surfaces are touched, the hands should be washed with soap and water before eating, drinking, smoking, or rubbing the eyes. Dead or diseased wildlife should be reported to state, tribal or federal natural resource agencies. Hunters should not handle or eat sick game, and should always wear rubber or latex gloves while handling and cleaning wild birds. The hands, as well as equipment and surfaces, should be thoroughly washed after dressing the carcass. All game should be cooked thoroughly.

If a human avian influenza pandemic occurs, additional precautions will be necessary. During a pandemic, crowded conditions and close contact with other people should be avoided. Respirators and other protective equipment may be advisable during close contact with an infected individual. In addition, infection control measures such as good hygiene, cancellation of social events and voluntary quarantine of infected individuals can limit the spread of disease.

Human vaccines for avian influenza have recently become available. One vaccine is now being manufactured and others are in development. These vaccines are not commercially available in the U.S. Instead, they are stockpiled by the government and will be distributed by public health officials if they are needed.

## Morbidity and Mortality

Symptomatic human infections with avian influenza viruses are rare. Although tens of millions of birds were infected with zoonotic H5N1 strains from 2003 to 2008, fewer than 400 human cases had been documented as of January 2009. Many infections have been reported in children and young adults. Most human infections seem to result from close contact with diseased or dead poultry. The risk of infection appears to be particularly high when slaughtering, defeathering or butchering birds, and while preparing them to cook. Exposure to chicken feces may have been the source of infection in a few children, and other routes of exposure have been reported or may be possible.

The severity of zoonotic influenza seems to vary with the virus subtype. More severe infections have been reported with the HPAI viruses, particularly avian H5N1. From 2003 through January 7 2009, 393 confirmed avian H5N1 infections, 248 of them fatal, were reported to WHO. These infections had a mortality rate of approximately 60-64%. It is possible that milder infections have also occurred, but have not been recognized or reported. Human disease has also been reported after infections with LPAI or HPAI H7N2, H7N3, H7N7 and H9N2 viruses. The reported infections with LPAI H9N2 viruses have resembled human influenza and been non-fatal. Most infections with the H7 viruses, including HPAI viruses, were limited to conjunctivitis, but influenza symptoms have also been seen. A single death occurred in an otherwise healthy veterinarian who became infected with a HPAI H7N7 virus.

Some evidence suggests that asymptomatic or mild, unrecognized infections can also occur. During an outbreak of LPAI H7N3 in 2003, 3.8% of poultry workers tested developed antibodies to H7 viruses. Antibodies to H5, H6, H7 and H11 avian influenza viruses have also been found in poultry workers and waterfowl hunters. Whether these antibodies result from infection or simply from exposure to antigens remains to be determined.

## Infections in Animals

### Species Affected

Avian influenza viruses mainly infect birds. Waterfowl and shorebirds appear to be the natural reservoirs for the influenza A viruses, and carry all of the known subtypes. The vast majority of viruses found in birds are LPAI; HPAI viruses are usually detected mainly in poultry. Some host specificity may be seen. For

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example, the gallinaceous birds including chickens, turkeys, quail, and pheasants often have severe infections with HPAI viruses, but the same viruses may cause only minor disease when they infect ducks, geese and other waterfowl. Among cage birds, most avian influenza virus infections have been recorded in passerine birds. Psittacine birds are rarely affected.

Two clades of H5N1 viruses are currently circulating in poultry. These viruses can infect and cause disease in many species of birds in addition to poultry. Unusually, they have caused severe disease and deaths in some species of wild waterfowl, which usually carry avian influenza viruses asymptotically. Most H5N1 viruses have been isolated from birds in the order Anseriformes, particularly the families Anatidae (ducks, swans and geese) and Charadriiformes (shorebirds, gulls and terns). Symptomatic infections have also been reported in pheasants, partridges, quail, guineafowl and peafowl (order Galliformes); egrets, storks and herons (order Ciconiiformes); pigeons (order Columbiformes); eagles, falcons and buzzards (order Falconiformes); owls (order Strigiformes); cranes, moorhens and sultans (order Gruiformes); cormorants (order Pelecaniformes), emus (order Struthioniformes), grebes (order Podicipediformes), budgerigars (order Psittaciformes) and flamingos (order Phoenicopteriformes). Symptomatic natural or experimental infections have been reported in passeriform birds including zebra finches, house finches, house sparrows, Eurasian tree sparrows, mynahs, crows, magpie robins, munias, orioles and magpies.

Some strains of avian influenza can cause disease in mammals including horses, mink, cats, dogs, ferrets, stone martens, palm civets, marine mammals and other species. Serologic evidence suggests that wild raccoons may also be infected with some viruses. The currently circulating avian H5N1 (HPAI) viruses seem to have a particularly broad host range. A few fatal avian H5N1 infections have been reported in zoo tigers, zoo leopards, housecats, captive palm civets, a dog and a stone marten. Experimental infections with avian H5N1 viruses have been established in housecats, dogs, foxes, pigs, ferrets, rodents, macaques, cattle and rabbits. These strains are continuing to evolve, and other species may also be susceptible to infection and/or disease.

## Incubation Period

The incubation period in poultry is one to seven days. The incubation period in mammals is also thought to be short.

## Clinical Signs

### *Birds*

In contrast to LPAI viruses, which usually cause asymptomatic infections, mild respiratory disease or decreased egg production, the HPAI viruses are highly virulent. These viruses can cause severe infections in some species of birds on a farm while leaving others

unaffected. The clinical signs are variable. Respiratory and systemic signs are often seen in chickens and turkeys. Sinusitis, lacrimation, cyanosis of the head, comb and wattle, edema of the head, and green to white diarrhea may be present in some birds. Hemorrhagic lesions may be found on the comb and wattles of turkeys. Other signs may include anorexia, coughing, sneezing, blood-tinged oral and nasal discharges, ecchymoses on the shanks and feet, neurologic disease, decreased egg production, loss of egg pigmentation and deformed or shell-less eggs. However, none of these clinical signs is pathognomonic, and sudden death can occur with few other signs. Most of the flock usually dies.

Clinical signs are minimal in ducks and geese infected with most HPAI viruses. In ducks, the most common signs are sinusitis, diarrhea and an increased mortality rate in the flock. However, some recent H5N1 isolates have caused severe, acute disease with neurological signs and high mortality rates in domesticated ducks. Some H5N1 viruses have also been associated with high mortality rates in wild migratory waterfowl. Experimental infections in call ducks (*Anas platyrhynchos* var. *domestica*), a cross between wild and domesticated ducks, resulted in drowsiness, ataxia, torticollis, circling and seizures. Experimental infections in wood ducks (*Aix sponsa*) caused severe weakness and incoordination, cloudy eyes, ruffled feathers, rhythmic dilation and constriction of the pupils, tremors, seizures and death. Other indigenous North American ducks including mallards (*Anas platyrhynchos*), northern pintails (*Anas acuta*), blue-winged teals (*Anas crecca*) and redheads (*Aythya americana*) remained asymptomatic when inoculated with the same strain. Swans have been severely affected by H5N1 viruses in Europe; these birds are generally found dead. Experimental infection with H5N1 viruses resulted in severe neurological disease in some mute swans and sudden death in others, while some birds shed virus subclinically.

Symptomatic infections with H5N1 have also been reported in experimentally infected gulls and passerine or psittacine birds. Laughing gulls (*Larus atricilla*) developed severe neurological disease; the signs included weakness, cloudy eyes, ruffled feathers, incoordination and torticollis. Most infected gulls died. One gull that recovered had a persistent head tilt; the other recovered completely. Anorexia and depression occurred in experimentally infected zebra finches, and 100% of the birds died within five days of inoculation. House finches and budgerigars developed anorexia, depression and neurologic signs, and died rapidly. In one study, H5N1 infections were mild in house sparrows, which experienced only mild depression and survived, and starlings, which remained asymptomatic. In another study, house sparrows but not starlings had severe, often fatal infections. Other subtypes can also be pathogenic. One H7N1 virus caused conjunctivitis, apathy and anorexia, with a high mortality rate, in canaries and a siskin.

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## ***Mammals infected with avian H5N1 viruses***

Symptomatic and asymptomatic avian H5N1 virus infections have been reported in some mammals. Fatal infections have been seen in tigers, leopards and housecats. Captive tigers and leopards exhibited respiratory distress and high fever before death. Little is known about the clinical signs in naturally infected housecats. One cat had fever, depression, dyspnea, convulsions and ataxia. Several infected housecats were found dead. One of these cats was apparently well up to 24 hours before its death. In experimentally infected cats, the clinical signs included fever, lethargy, conjunctivitis, protrusion of the third eyelid, dyspnea and death. Recently, asymptomatic infections were reported in housecats that had been accidentally exposed to a sick, H5N1-infected swan.

Other carnivores may also be affected. A dog that ate H5N1-infected poultry developed a high fever, panting and lethargy, and died the following day. Experimentally infected dogs have been asymptomatic or developed only transient fever and conjunctivitis. Some experimentally infected foxes developed fever but no other clinical signs; however, lung lesions were reported at necropsy. Experimental avian H5N1 virus infections in ferrets ranged from mild upper respiratory infections to severe, fatal disease; the pathogenicity varied with the specific isolate. The clinical signs in severe cases included high fever, extreme lethargy, anorexia, weight loss and diarrhea. Some infections in ferrets were fatal.

Avian H5N1 infections in pigs appear to be mild or asymptomatic. Mild respiratory signs including coughing, fever and transient anorexia were observed in some experimentally infected pigs, while others experienced slight, temporary weight loss but no other clinical signs. Miniature pigs were resistant to infection in one study. Cattle inoculated with high titers of H5N1 virus isolated from infected cats remained asymptomatic but could transiently shed virus.

## ***Mammals infected with other subtypes***

Infections with other subtypes of influenza A viruses have been associated with outbreaks of pneumonia in seals and disease in a pilot whale. The viruses appeared to be of avian origin. The clinical signs in seals included weakness, incoordination, dyspnea and swelling of the neck. A white or bloody nasal discharge was seen in some animals. In the single known case in a whale, the clinical signs were extreme emaciation, difficulty maneuvering and sloughing skin.

## **Communicability**

Avian influenza viruses are transmitted readily between birds. Virus shedding can begin as early as 1 to 2 days after infection. Most chickens shed LPAI influenza viruses for only a week, but a minority of the flock can excrete the virus in the feces for up to two weeks. Birds infected with HPAI viruses usually die before this time.

Ducks can shed large quantities of influenza viruses asymptotically, and they may shed the virus for up to 30 days. Transmission from birds to mammals seems to be uncommon.

As of January 2009, animal-to-animal transmission has been reported only in housecats and their wild relatives. Cats experimentally infected with the avian H5N1 virus shed the virus by the third day post-inoculation, and were able to infect two sentinel cats in close contact. Naturally infected, asymptomatic cats appeared to excrete virus only sporadically, and for less than two weeks. Horizontal transmission was not observed in this instance. Cats appear to shed avian influenza viruses from the intestinal tract as well as the respiratory tract. Limited animal-to-animal transmission has also been reported among tigers in a zoo.

Other species can also shed HPAI viruses, but horizontal transmission has not been reported. In experimentally infected foxes, avian H5N1 virus was detected in both respiratory secretions and feces. In experimentally infected dogs, pigs and cattle, this virus has been found only in respiratory secretions. In cattle, the shedding was transient and occurred after high dose inoculation with a virus isolated from cats. Sustained or prolonged transmission has not been reported with avian H5N1 viruses in any mammal including cats.

## **Post Mortem Lesions** [Click to view images](#)

The lesions in chickens and turkeys are highly variable and can resemble other avian diseases. There may be subcutaneous edema of the head and neck, fluid in the nares and oral cavity, and severe congestion of the conjunctivae. Hemorrhagic tracheitis can be seen in some birds; in others, the tracheal lesions may be limited to excess mucoid exudate. Petechiae may be found throughout the abdominal fat, serosal surfaces and peritoneum. Hemorrhages may also be seen on the mucosa of the proventriculus, beneath the lining of the gizzard, and in the intestinal mucosa. The kidneys can be severely congested, and are sometimes plugged with urate deposits. The ovaries may be hemorrhagic or degenerated, with areas of necrosis. The peritoneal cavity often contains yolk from ruptured ova. Severe airsacculitis and peritonitis may be seen in some birds. Birds that die peracutely and young birds may have few or no lesions.

Experimentally infected wood ducks had multiple petechial hemorrhages in the pancreas. More extensive lesions were reported in experimentally infected laughing gulls; in these birds, petechial hemorrhages were found in the ventriculus, apex of the heart, cerebrum and pancreas. In naturally infected swans, the most consistent lesions are multifocal hemorrhagic necrosis in the pancreas, subepicardial hemorrhages, and pulmonary congestion and edema. Mild or absent gross lesions were reported in experimentally infected zebra finches, house finches and budgerigars despite high mortality rates in these species.

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Pulmonary edema and pneumonia; conjunctivitis; cerebral, renal and splenic congestion; multifocal hepatic necrosis; hemorrhages in the intestinal serosa, lymph nodes, perirenal tissue and/or diaphragm; and severe hemorrhagic pancreatitis have been reported in naturally infected cats. Multiple to coalescing foci of pulmonary consolidation were reported in experimentally infected cats. The pulmonary lesions were similar whether the cats were infected intratracheally or by the ingestion of infected chicks. In one study, cats infected by ingestion also had enlarged tonsils, which contained multifocal petechial hemorrhages, and enlarged mandibular and/or retropharyngeal lymph nodes. Petechial hemorrhages occurred in the liver of some cats. In one cat, the liver lesions were accompanied by generalized icterus.

In naturally infected tigers and leopards, the gross lesions included severe pulmonary consolidation and multifocal hemorrhages in multiple organs including the lung, heart, thymus, stomach, intestines, liver and lymph nodes. Bloody nasal discharge, severe pulmonary congestion and edema, and congestion of the spleen, kidney and liver were reported in a dog. Pulmonary lesions including interstitial pneumonia have been reported in some experimentally infected pigs. Experimentally infected foxes also developed lesions mainly in the lung. Some foxes inoculated intratracheally had histopathologic evidence of encephalitis and myocarditis, but these lesions were not seen in foxes fed infected tissues.

## Diagnostic Tests

Avian influenza can be diagnosed by virus isolation. The virus can be recovered from oropharyngeal and/or cloacal swabs in live birds. Feces can be substituted in small birds if cloacal samples are not practical. Oropharyngeal or cloacal swabs (or intestinal contents), and pooled or individual organ samples (trachea, lungs, air sacs, intestine, spleen, kidney, brain, liver and heart) are tested in dead birds. Virus isolation is performed in embryonated eggs; hemagglutinating activity indicates the presence of influenza virus. The identity of the virus can be confirmed with agar gel immunodiffusion (AGID) or ELISAs. The virus is subtyped with specific antisera in AGID or hemagglutination and neuraminidase inhibition tests. An immunofluorescence assay was used to identify the neuraminidase type during an outbreak in Italy. Virulence tests in susceptible birds, together with genetic tests to identify characteristic patterns in the hemagglutinin, are used to differentiate LPAI from HPAI viruses.

RT-PCR assays can identify avian influenza viruses in clinical samples, and can replace virus isolation in some cases. These tests can also distinguish some subtypes. Real-time RT-PCR is the method of choice in many laboratories. Viral antigens can be detected with ELISAs including rapid tests. As of 2008, the World Organization for Animal Health (OIE) recommended that

antigen detection tests be used to identify avian influenza only in flocks and not in individual birds.

Serological tests including agar gel immunodiffusion, hemagglutination, hemagglutination inhibition and ELISAs are useful as supplemental tests. Although most poultry and other susceptible birds die before developing antibodies, serology can be valuable for surveillance and to demonstrate freedom from infection. AGID tests can recognize all avian influenza subtypes in poultry, but hemagglutination inhibition tests are subtype specific and may miss some infections. In wild birds, some serologic tests may underestimate the prevalence of H5N1 infections.

## Treatment

In most countries including the U.S., high pathogenicity avian influenza in poultry is not treated; outbreaks are controlled by eradication.

## Prevention

Poultry can be infected by contact with newly introduced birds or fomites, as well as by contact with wild birds, particularly waterfowl. The risk of infection can be decreased by all-in/all-out flock management, and by preventing any contact with wild birds or their water sources. Birds should not be returned to the farm from live bird markets or other slaughter channels. In addition, strict hygiene and biosecurity measures are necessary to prevent virus transmission on fomites.

Outbreaks can be controlled by rapid depopulation of infected and exposed flocks, proper disposal of carcasses and contaminated materials, and strict biosecurity measures. Farms should be quarantined, and movement controls and surveillance should be established. Infected premises must be thoroughly cleaned and disinfected. Insects and mice on the premises should be eliminated, then the flock depopulated and the carcasses destroyed by burying, composting or rendering. Once the birds have been killed, the manure and feed should be removed down to a bare concrete floor. If the floor is earthen, one inch or more of soil should be removed. The manure can be buried at least five feet deep. It may also be composted for 90 days or longer, depending on the environmental conditions. The compost should be covered tightly with black polyethylene sheets to prevent the entry of birds, insects and rodents. Feathers can be burned or composted; alternatively, they may be removed and the area wet down with disinfectant. High-pressure spray equipment should be used to clean all equipment and building surfaces. Once all surfaces are clean and free of all organic material, the entire premises should be sprayed with an approved residual disinfectant.

HPAI vaccines are not used routinely in the U.S. or most other countries; however, nations may consider vaccination as a preventative or adjunct control measure during an outbreak. Avian vaccines are usually autogenous or from viruses of the same subtype or

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hemagglutinin type. Currently licensed vaccines in the U.S. include inactivated whole virus and recombinant fowlpox- H5 vaccines. The use of these vaccines requires the approval of the state veterinarian and, in the case of H5 and H7 vaccines, USDA approval. Because vaccines can allow birds to shed virus while remaining asymptomatic, good surveillance and movement controls are critical in a vaccination campaign. Methods used to recognize infections with field viruses in vaccinated flocks include a “DIVA” (differentiating vaccinated from infected animals) strategy, and the use of sentinel birds. Vaccination may place selection pressures on avian influenza viruses, and might eventually result in the evolution of vaccine-resistant isolates.

Mammals should not be fed poultry or other birds that may be infected with H5N1 avian influenza viruses. They should also be kept from contact with potentially infected flocks and wild birds. During outbreaks, cats and dogs should be kept indoors whenever possible.

## Morbidity and Mortality

In domesticated poultry (particularly chickens), HPAI viruses are often associated with morbidity and mortality rates that approach 90-100%. Any survivors are usually in poor condition and do not begin laying again for several weeks. Ducks and geese are clinically unaffected by many HPAI viruses.

Avian influenza virus infections in wild birds are typically asymptomatic; however, some of the currently circulating H5N1 viruses have resulted in high mortality rates in wild birds. In April 2005, an outbreak at Qinghai Lake in central China resulted in the deaths of more than 6000 migratory wild birds. H5N1 viruses have also been isolated from dead migratory birds, including waterfowl, in a number of other countries. High mortality rates have been reported in some but not all experimentally infected wild birds. All six laughing gulls infected with recent strains of H5N1 became severely ill, and four died. Four of six infected wood ducks also became severely ill while two others remained asymptomatic. Three of the sick ducks died and one recovered. Mallard, northern pintail, blue-winged teal and redhead ducks inoculated with the same viral strains did not become ill.

Morbidity and mortality rates in passerine and psittacine birds have varied with the species. In one study, mortality rates approached 100% in experimentally infected zebra finches, house finches and budgerigars, but all house sparrows experienced mild disease and survived, and all starlings remained asymptomatic. In a study with a different H5N1 virus, the mortality rate was 66-100% in house sparrows, but no deaths were seen in starlings.

The morbidity and mortality rates in cats or dogs infected with avian influenza viruses are unknown. In an unpublished study from Thailand, antibodies to H5N1 viruses were found in 8 of 11 cats and 160 of 629 dogs. In contrast, no antibodies were found in 171 cats from areas

of Austria and Germany where H5N1 infections had been reported in wild birds. Fatal infections with avian H5N1 viruses have been reported in housecats, a dog, tigers and leopards. Experimentally infected cats also exhibited severe disease and high mortality rates. However, asymptomatic infections were reported in cats that had been exposed to an infected swan in an animal shelter. Few of the latter cats shed virus, and none became ill despite the presence of other viral and bacterial infections, and high stress levels in this population. Asymptomatic and mild H5N1 infections have been reported in experimentally infected dogs. Pigs do not seem to be very susceptible to this virus, although asymptomatic infections can occur.

## Internet Resources

- Centers for Disease Control and Prevention. Avian Influenza  
<http://www.cdc.gov/flu/avian/>
- Public Health Agency of Canada. Material Safety Data Sheets  
<http://www.phac-aspc.gc.ca/msds-ftss/index.html>
- The Merck Manual  
<http://www.merck.com/pubs/mmanual/>
- The Merck Veterinary Manual  
<http://www.merckvetmanual.com/mvm/index.jsp>
- United States Animal Health Association. Foreign Animal Diseases.  
[http://www.vet.uga.edu/vpp/gray\\_book02/fad/index.php](http://www.vet.uga.edu/vpp/gray_book02/fad/index.php)
- United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). Avian Influenza.  
[http://www.aphis.usda.gov/newsroom/hot\\_issues/avian\\_influenza/avian\\_influenza.shtml](http://www.aphis.usda.gov/newsroom/hot_issues/avian_influenza/avian_influenza.shtml)
- USDAAPHIS. Avian Influenza Portal  
[http://www.usda.gov/wps/portal/!ut/p/\\_s.7\\_0\\_A/7\\_0\\_1OB?navid=AVIAN\\_INFLUENZA&navtype=SU](http://www.usda.gov/wps/portal/!ut/p/_s.7_0_A/7_0_1OB?navid=AVIAN_INFLUENZA&navtype=SU)
- USDA APHIS. Biosecurity for the Birds  
[http://www.aphis.usda.gov/animal\\_health/birdbiosecurity/](http://www.aphis.usda.gov/animal_health/birdbiosecurity/)
- United States Geological Survey (USGS). National Wildlife Health Center. List of species affected by H5N1 (avian influenza)  
[http://www.nwhc.usgs.gov/disease\\_information/avian\\_influenza/affected\\_species\\_chart.jsp](http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp)
- World Health Organization. Avian Influenza  
[http://www.who.int/csr/disease/avian\\_influenza/en/](http://www.who.int/csr/disease/avian_influenza/en/)
- World Organization for Animal Health (OIE)  
<http://www.oie.int>
- OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals  
[http://www.oie.int/eng/normes/mmanual/a\\_summry.htm](http://www.oie.int/eng/normes/mmanual/a_summry.htm)
- OIE Terrestrial Animal Health Code  
[http://www.oie.int/eng/normes/mcode/A\\_summry.htm](http://www.oie.int/eng/normes/mcode/A_summry.htm)

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